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Autologous Bone Marrow Transplantation (ABMT)

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Public Health Service Assessment

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INTRODUCTION

Autologous bone marrow transplantation is a process in which a portion of a patient's own bone marrow is obtained by needle aspirations usually from the iliac crest and placed in storage to be infused intravenously after the patient has been treated with a marrow-ablative regimen of chemotherapy and/or radiotherapy given for the purpose of treating his malignancy. The transplanted marrow serves as the source of lymphoid and hematopoietic stem cells. It serves to repopulate the marrow for hematopoietic functions and to generate circulating cells.

Increasing evidence suggests that the response of malignant tumors is improved by higher than conventional doses of chemotherapy or radiotherapy. In an attempt to circumvent the dose-limiting effects of bone-marrow toxicity seen with radiotherapy and many chemotherapeutic agents, bone marrow transplantation has been used to "rescue" patients from otherwise lethal or highly toxic therapy. Autologous marrow is intended to avoid the potentially fatal graft-versus-host disease which is associated with allogeneic marrow transplantation. It also avoids problems associated with finding a suitable donor.

The procedure is usually performed by specially trained hematologists and oncologists in institutions experienced in the use of "supralethal" chemo-radiotherapy and in bone marrow transplantation.

BACKGROUND

The clinical application of bone marrow transplantation for the treatment of otherwise fatal blood diseases began in 1957 (1). At that time, six laboratory workers who were heavily irradiated as a consequence of a nuclear reactor accident in France were treated by the infusion of large amounts of donor marrow. In the following decade, approximately 200 patients received bone marrow transplants for a variety of diseases. The results of these transplantation efforts were extremely poor. Patients survival was one percent. These poor results led to a virtual moratorium on bone marrow transplantation. In the early 1970's animal experimentation led to the development of adequate pre-transplant "conditioning" regimens and improved post-transplant care, resulting in renewed interest and improved outcomes in clinical bone marrow transplantation (2).

The replacement of abnormally functioning marrow with stem cells capable of self-replication and differentiation is now technically feasible. In the employment of allogeneic transplants,difficulties in locating appropriately matched HLA-donors, the development of acute or chronic graft-vs-host disease (GVHD), with their significant morbidity and mortality, proved to be major obstacles to the widespread use of bone marrow transplantation. Successful engraftment of marrow depends on the number of stem cells infused and on suppression of host immunity to prevent graft rejection (3). Frequently, the techniques used for immunosuppression lead to another problem, that of infection in the immunocompromised host. The commonly used treatment regimens for allogeneic transplants include high-dose chemotherapy, total body irradiation and anti-thymocyte globulin, used alone or in combination (4).

Under the best of circumstances, the use of allogeneic bone marrow transplantation has resulted in a mortality rate of 30-40 percent due to transplant related complications (GVHD and infection) or the recurrence of the primary disease (5). The identification of the major histocompatibility loci for improved matching of

donor and recipients, and the development of sophisticated patient support systems, have served to advance bone marrow transplantation. Only the use of syngeneic or autologous marrow avoids most of these complications. The diffusion of this technology is limited to the relatively few institutions worldwide which have the level of expertise required to perform these procedures.

The revived interest in bone marrow transplantation arose in 1977 after reported success in treating patients with acute leukemia using intensive chemotherapy and total body irradiation followed by marrow transplantation from HLA identical siblings (6).

The use of autologous marrow for transplantation could permit the extension of this technology to a larger number of patients. It would avoid GVHD and the need for iatrogenic immunosuppression and its associated complications.

The successful outcome of autologous bone marrow transplantation (ABMT) depends upon eliminating the patient's tumor by marrow oblative chemo-radiotherapy followed by reinfusion of previously stored tumor-free marrow containing a sufficient number of stem cells to restore normal marrow function.

DESCRIPTION

ABMT is used to "rescue" patients from bone marrow "failure" caused by high-dose chemotherapy and/or total body irradiation used in the treatment of cancer (7). In general, the transplant procedure can be described in six phases (8):

1. harvesting the patient's marrow,
2. high-dose chemo-radiotherapy (cytotoxic treatment)
3. marrow grafting,
4. pancytopenic phase,
5. early recovery,
6. convalescence.

Marrow Harvesting

Prerequisites for successful ABMT include the ability to obtain sufficient marrow to reconstitute hematologic function and the successful pre-transplant treatment of the patient.(9).

Bone marrow is usually obtained by multiple (50-100) marrow aspirations from the iliac crests and rims of the ilia of the donor. The procedure requires hospitalization and is performed under spinal or general anesthesia with little associated morbidity other than moderate to significant pain at the aspiration sites which persists for several days (9,10). Life threatening complications, occurred in 9 of 3,290 reported procedures, a frequency of 0.27 percent. These included non-fatal cardiac arrest, pulmonary embolism, aspiration pneumonitis, ventricular tachycardia and cerebral infarction. The death of a donor has been reported due to a cardiac arrest during induction of general anesthesia. Other adverse consequences of marrow donation included bleeding, requiring transfusion, one case of a broken aspiration needle requiring surgical removal and a few transient episodes of hypotension, atrial arrythmia or laryngospasm (10). In adults 400-1,500 ml of marrow is obtained which represents $2x10^{10}$ nucleated cells.

The marrow is mixed with heparin and tissue culture medium and filtered to remove larger particles. Either fresh marrow (3-4 days viability) or marrow cryopreserved and stored in liquid nitrogen (for up to 3 years or more) can be used for the transplants (11,12). The only cells capable of restoring marrow function are the pluripotent stem cells. These represent fewer than one percent of the heterogeneous of marrow cells obtained by aspiration.

Cytotoxic Therapy

The pretransplant preparations of patients varies according to their disease and are determined by the type of stem cells present in the patient's marrow (13). Patients with severe combined immunodeficiency disease (SCID) have absent or defective lymphoid stem cells and in most cases require no immunosuppression. Commonly used preparative regimens for allogeneic transplants include the use of cyclophosphamide,

irradiation, antihuman thymocyte serum and busulfan either alone or in combination to insure immunosuppression and adequate myeloablation to provide "space" for the transplanted marrow (13,14). The concept of "space" also includes the non-immunologic microenvironmental factors necessary for engraftment (15). The treatment regimens for patients usually require 7 days of pretransplant hospitalization (16).

Marrow Grafting

The minimum dose of marrow for successful transplantation has been experimentally estimated to be between 0.1-0.7 percent of the total body marrow or 0.1-0.8x10^8 nucleated cells per kilogram of body weight. Clinically, 1-5x10^8 nucleated cells per kilogram are infused intravenously and larger doses have only a slight effect on subsequent engraftment. After ABMT, engraftment is assumed by either the appearance of discrete colonies of hemotopoietic cells in the marrow as early as 14 days post-transplant or by the presence of increasing peripheral leucocyte and platelet counts seen within 21-35 days (14).

Pancytopenic Phase

Patients are profoundly thrombocytopenic and granulocytopenic during the first two to four weeks post-transplant. They are subject to fevers, bacterial infections and bleeding episodes. As high as 10 percent of good-risk patients may die of bleeding or infection despite the routine use of antibiotics and/or platelets and white cell infusions (14,15).

Early Recovery

Approximately 4 weeks following the transplant, white blood cell counts are usually normal and platelet transfusions are no longer required in 70-80 percent of patients (16). However, the reconstitution of marrow function does not necessarily mean reconstitution of immune function, which may be delayed for more than 12 months. In patients that have normal blood counts and no evidence of infection discharge from hospital can usually be expected 4 weeks post transplant. Despite normal white cell counts, during the first three months after grafting, patients continue to be at risk for

developing almost any type of infection.

Convalescence

During convalescence both erythroid and myeloid elements approach normal. Absolute lymphocyte counts are usually normal in two to three months, but the number of T-helper cells and skin test reactivity are frequently abnormal for as long as twelve months. During this time the patient continues to be at risk for opportunistic infections.

Features Unique to ABMT

Prerequisites for performing successful ABMT include the ability to obtain sufficient marrow to reconstitute hematologic function, while assuring the absence of clonogenic tumor cells in the graft (9). The most pressing problem is "purging" the harvested marrow of tumor cells that may be present. This is currently being studied by a variety of techniques including physical separation, immunologic manipulations, and pharmacologic treatments.

On the basis of information which suggests that the density of leukemic blast cells are different from normal stem cells, attempts have been made to separate these cells using discontinuous albumin gradients (9). Immunologic manipulations designed to eliminate tumor cells from marrow in vitro have included the use of cell binding antibody or antigen covalently bound to plant or bacterial toxin. This technique has been effective in mouse models for the killing of leukemic cells in bone marrow (19). Also effective is the use of heterologous cytotoxic antisera or antithymoctye globulin as well as monoclonal anti T-cell antisera (9). Although pharmacologic methods for eliminating tumor cells in vitro from tumor stem cell mixtures have not been extensively investigated, a recent report suggested that 4-hydro-peroxycyclophosphamide (4HC) may be able to eliminate rat AML tumor cells from a normal marrow-tumor cell suspension (12).

RATIONALE

The rationale for bone marrow transplantation is that high doses of chemotherapy and/or radiotherapy required to kill all or most tumor cells will frequently result in lethal marrow aplasia. This can be reversed ("rescued") by the transplantation of stored autologous marrow cells which will repopulate the patients' bone marrow and provide a renewed source of normal cells.

Preclinical studies have demonstrated a steep dose-response curve for most therapeutic regimens. In the rodent osteogenic sarcoma, 5-fluorouracil at a dose of 66 mg/kg every four days achieves a 70 percent complete response rate. A reduction of dose to 55 mg/kg on the same schedule reduces the complete response rate to 0.1 percent. At lower doses no responses are observed (17,18). In general, the number of tumor cells surviving exposure to a chemotherapeutic agent declines as a logarithmic function of drug concentration (11). Increasing the dose of chemotherapy and/or radiotherapy in the treatment of patients with cancer has resulted in increased tumor response rates. For Hodgkin's disease and non-Hodgkin's lymphoma, a twofold difference in the dose of an alkylating agent plus methotrexate results in a three to five fold difference in the proportion of patients in whom an antitumor effect is seen (19). In a randomized study of dosage effects on fluorouracil in colon and breast cancers, it was found that a 50 percent increase in dose resulted in a 33 percent response rate as compared to a 15-20 percent response rate seen with standard doses (20). However, dose-limiting myelotoxicity has proven to be a major factor in preventing the successful exploitation of this concept. Attempts to circumvent the dose-limiting myelotoxicity of these therapies includes protective environments, platelet and granulocyte transfusions, antibiotics, and more recently, a renewed interest in bone marrow transplantation (6,7).

The use of autologous rather than allogeneic marrow provides the advantage of avoiding the complications of graft-vs-host disease and the iatrogenic immunosuppression. The technique can be used for patients who do not have an

appropriate HLA matched donor. Graft-vs-host disease (GVHD) is a clinical syndrome resulting from the reaction of immunologically competent lymphocytes introduced from a donor into a non-syngeneic receipient. Although there is a histocompatibility difference the recipient is unable to mount an immunologic attack against the donor's cells (21). The result is that the donor T cells attack and reject the recipients body. The disease is characterized by fever, rash, hepatitis, diarrhea, pancytopenia infection carditis, and multiple organ systems failure. It is recognized as a frequent consequence of allogeneic bone marrow transplantation and in its acute form seen within 1-4 weeks after engraftment. It has been reported to occur in 50-75 percent of cases. The chronic form of GVHD develops 2-12 months post-transplant and can be observed in 30-50 percent of patients post allogeneic BMT (21). These problems are avoided by the use of autologous marrow.

An outline of the procedures commonly used for ABMT "rescue" after high dose chemo-radiotherapy is as follows (11):

1. conventional cancer therapy is given to the patient to induce a remission,
2. patients' bone marrow is stored during remission,
3. marrow ablative is given if the patient relapses,
4. ABMT is given as a "rescue" if marrow failure results from supralethal therapy.

REVIEW OF AVAILABLE INFORMATION

Clinical trials employing marrow-lethal doses of chemotherapy and/or radiotherapy demonstrate consistent hematologic recovery using cyropreserved autologous marrow. In a clinical trial involving 14 patients treated with high dose vincristine cyclophosphamide and total body irradiation designed to treat resistant cancers (8), all patients developed granulocyte counts of $0.2X10^9$/litre or less and platelet counts of $20X10^9$/litre or less immediately following treatment. Marrow recovery after transplantation was seen in all seven patients who survived 30 days or

more. Granulocyte counts were $0.5X10^9$/litre or more by a median of 19 days post-transplant. Platelet counts were $20X10^9$/litre or more by a median of 24 days post-transplant. Another trial involved 18 patients with small cell carcinoma of the lung who were treated with high dose chemotherapy alone, as well as 4 patients with acute myelogenous leukemia treated with high dose chemotherapy and total body irradiation (27). Infusions of stored autologous marrow produced recovery of granulocytes to greater than $1X10^9$/litre with platelet counts greater than $100X10^9$/litre in all surviving cancer patients by a median of 17.5 days. The hematologic reconstitution was slower but acceptable in the leukemic patients who had more than $1X10^9$/litre of granulocytes between 26 and 40 days and greater than $20X10^9$/litre of platelets between 23 and 77 days. Myelotoxic doses of chemotherapy were 3 to 5 times the standard dose, while marrow lethal radiotherapy was usually 800-1,000 rads of total body irradiation in a single fraction or 1,200-1,400 rads split-fraction given at a rate of 5-20 rads/min (9,11).

ABMT has been widely applied to other malignancies known to be sensitive to chemotherapy and radiotherapy in addition to leukemias and lymphomas. Cancers that are highly sensitive to cytoreductive therapy i.e., those with high growth fractions unfortunately have a high probability of marrow involvement at the time of diagnosis (leukemia, lymphoma and small cell lung cancer) (9). Tumors suitable for ABMT would be those that infrequently involve the marrow. Retrospective reviews of bone marrow biopsies for various tumor types indicate a high variability of marrow involvement. Lung and breast cancers represent a relatively high rate and for testicular, ovarian, and cervical cancers a relatively low incidence of marrow involvement (23,24).

Early clinical studies using ABMT included patients with a variety of tumor types. The first clinical study was performed in 1958 when Kurnick et al. reported treating two patients with metastatic pulmonary disease with intensive radiotherapy and reinfusions of stored autologous marrow (25). The patient with testicular carcinoma appeared to clinically improve and survived for four months before dying of metastatic disease. The one with renal carcinoma failed to show any benefit and died on the tenth

post-transplant day. Two case reports from England in 1959 reported on patients who underwent similar treatments (26). The first, a patient with pulmonary metastasis from an osteogenic sarcoma achieved a clinical improvement for two months following irradiation and ABMT but died of respiratory failure ten weeks post transplant. The second patient had pulmonary metastasis from a Ewing's sarcoma of her ischium. She experienced a complete response with no evidence of disease at the time of the report.

McGovern et al. (27) were the first to employ ABMT in the treatment of leukemia. They reported on three children with acute lymphocytic leukemia in relapse who had total body irradiation and marrow stored during a remission. Two of the three died without evidence of engraftment, but the third had a complete response.

In a series of 7 patients with acute myelogenous leukemia in relapse treated with high-dose chemotherapy and total body irradiation, all patients achieved complete remissions but subsequently relapsed within 5-13 months (12). The effectiveness of ABMT is limited by the degree to which pretransplant therapy succeeds in killing most or all tumor cells (9).

Early trials used high dose chemotherapy rather than irradiation for the treatment of cancer. McFarland et al. (28) treated three patients with disseminated Hodgkin's disease with high dose nitrogen mustard (over 1.0 mg/kg). Clifford et al. (29) treated three African children with Burkitt's lymphoma with high-dose nitrogen mustard and ABMT. In the McFarland report, two of the five patients succumbed to infection and the remaining three had hematological recovery following ABMT and experienced brief remissions. The three Burkitt's patients treated by Clifford all had symptomatic relief and regression of tumor size. The results of these early cases were generally regarded as unsuccessful, primarily because of incomplete or only short-term responses. However this may well reflect the ineffectiveness of single agent chemotherapy in Hodgkin's disease regardless of marrow support techniques.

Leukemia

Using single agent high-dose chemotherapy Maraninchi et al. (30) reported seven cases of relapsed acute leukemia treated with high-dose melphalan and ABMT. All patients achieved complete remission. At M.D. Anderson Hospital (31), eight patients with acute lymphocytic leukemia (ALL) in second or third relapses were treated with piperazinedione and total body irradiation (TBI) in preparation for ABMT. Four patients of the eight achieved a complete remission having a median duration of five months.

Using multiple drug combinations, investigators at M.D. Anderson Hospital (32) treated patients with ALL in first remission with cyclophosphamide, BCNU and VP16 followed by ABMT. Two of six patients in relapse who had previously failed attempts to reinduce remission with conventional treatment achieved complete remissions lasting six and seven months.

In treating acute mylelogenous leukemia (AML) in Seattle (33) thirteen patients were treated with cyclophosphamide and TBI followed by ABMT after first remission. There was one early death due to septicemia. Eight patients relapsed and died (median survival 335 days). Three patients continued in complete remission 22-47 months after transplant. In this small series the number of long-term survivors was not superior to that expected with conventional chemotherapy.

Thus far, treatment of chronic myelogenous leukemia (CML) with autologous stem cells, has not been shown to be curative and ABMT has been shown to only maintain the chronic phase of the disease. In a recent review of results in 42 patients from 15 centers worldwide (34), six of eight cases that received ABMT demonstrated delayed engraftment and died of infection or hemorrhage. Thirty-four patients were transplanted with autologous peripheral blood cells and engraftment was successful in 33. Median survival was six months. The median duration of the second chronic phase was only 14 weeks. These results are unsatisfactory primarily because of the rapid relapse of the blastic phase. There has been no reported experience using ABMT in the chronic phase of CML.

A review of the published experience of ABMT in the treatment of leukemia included the following data (12):

Number of patients		Results	Remission Duration
AML			
(relapse)	34	27 complete responses	3-14 months
(remission)	35	18 in continued remission	2-20 months
ALL			
(relapse)	16	8 complete responses	2-14 months
(remission)	22	16 in continued remission	1-43 months

Lymphomas

Spitzer et al. (35) reviewed the published experience of high-dose chemotherapy with ABMT in treating patients with lymphomas who relapsed after chemotherapy. (See table below)

Number of patients		Complete Response	Remission Duration
Relapsed Hodgkin's Disease	31	17	9-27 plus months
Non-Hodgkins Lymphoma	80	42	1-60 plus months

Recent data from the Memorial Sloan-Kettering Cancer Center (36) reported on 10 of 22 patients with poor prognosis non-Hodgkin's lymphoma who achieved complete responses lasting 7-37 months following ABMT and high-dose chemotherapy.

Solid Tumors

The long term disease free survival of Stage III and IV neuroblastoma is approximately 10-20 percent. Secondary responses after relapse are rare. The recent report (40) of long term responses and possible cures with high-dose melphalan, total body irradiation, standard doses of Adriamycin and VM-26 appears encouraging. A randomized study will be required to compare this therapy with continued combination chemotherapy before definitive conclusions as to efficacy can be formed.

High-dose chemotherapy with ABMT is being investigated in patients with Ewing's

Sarcoma and a poor prognosis aiming at obtaining remission (35,37). Current short-term followup suggests fewer relapses than reported in previous studies, but further experience is needed before a definite conclusion concerning efficacy can be made.

The use of ABMT in retinoblastoma and rhabdomyosarcoma was undertaken in pilot studies with too few patients to be meaningfully interpreted (38).

A compilation of results of ABMT for childhood malignancies other than leukemia can be seen in the following table:

Number of Patients		Complete Response	Remission Duration
Neuroblastoma	9	7	4-44 months
Ewing's Sarcoma	14	5	3-14 months
Rhabdomyosarcoma	4	2	3-6 months
Retinoblastoma	2	1	2 months

Other solid tumors for which published data exist include the following:

Number of patients		Complete Responses	Remission Duration
Melanoma	88	16	1-30 months
Small Cell Lung Cancer	168	69	1-42 months
Glioma	50	15 (clinically improved)	4-41 months
Breast Cancer	21	4	5-6 months
Testicular Cancer	13	4	1-5 months

High-dose chemotherapy and ABMT in treating melanoma has produced both partial and complete responses with total response rates (partial plus complete) of 50 percent (35,39). Second remissions induced by standard chemotherapy, are very uncommon in this condition. Some remissions have been documented for periods exceeding one year, but further followup is required to establish how sustained these remissions may be.

There is more experience with ABMT in small cell cancer of the lung than with any other solid tumor type (35). The large number of chemotherapy combinations applied in this condition with and without irradiation, and the stages of disease in which

treatment is applied added to the short followup of most patients make the effectiveness of these therapies impossible to evaluate.

The overall response rate to ABMT in relapsing gliomas is approximately 30 percent (35), which is similar to that achieved with standard chemotherapy. Difficulties in evaluating anti tumor responses in cases of glioma and the small number of patients treated with high-dose chemotherapy and ABMT also makes it difficult to evaluate the role of ABMT in this disease. Too few patients with relapsed breast or testicular cancers have been treated with high-dose chemotherapy and ABMT to allow for a proper evaluation of its efficacy (35,40).

DISCUSSION

Renewed interest in ABMT closely followed the reports of successes of allogeneic bone marrow transplantation in the treatment of leukemia. Thomas et al. (41) reported on one hundred patients with acute leukemia treated by chemotherapy, total body irradiation and allogeneic marrow transplants. These patients with refractory leukemia achieved almost a 15 percent cure rate. Such studies confirmed the ability of bone marrow transplantation to prevent lethal myelosuppression resulting from pretransplant chemotherapy.

The first convincing proof of the efficacy of ABMT to provide recovery of marrow function following lethal total body irradiation was the study by Dicke et al. (31) in which 28 patients with refractory acute leukemia were treated with a combination of piperazinedione and total body irradiation. Hematological recovery was evaluable only in the 12 patients who achieved a remission with granulocytes exceeding 0.5×10^9/ml achieved by an average of 21 days following transplantation. Platelets exceed 21×10^9/ml by an average of 22 days.

The increasing application of ABMT for the treatment of malignancies is a reflection of its clinical acceptability in the major bone marrow transplant centers. The

procedure is relatively safe when applied under circumstances where it is employed as a treatment of last resort.

If myelotoxicity can be fully overcome by ABMT, other toxicities may become problematic. Cardiomyopathy, interstitial pneumonitis, hepatotoxicity, hemorrhagic cystitis, intestinal and oral mucostitis to mention only a few complications of intensive therapy all require extensive support services. In a series of 143 patients with refractory cancer treated with high-dose BCNU and ABMT (42), recovery from severe pancytopenia occurred in less than 4 weeks post transplant in 93 percent of patients, suggesting the efficacy of the ABMT in restoring marrow function. However, serious extramedullary toxicity was seen with dosages of 1,200 mg/m^2, of the drug. A 9.5 percent incidence of fatal interstitial pneumonitis and a 3 percent incidence of fatal hepatic necrosis was observed. Higher doses (1,500-2,850 mg/m^2) were associated with a 35 percent incidence of fatal hepatotoxicity. Two patients experienced fatal encephalomyelopathy. One patient who received the highest cumulative dose of BCNU (3,450 mg/m^2) died of cardiac necrosis. In a recent study, (43) 25 previously untreated patients with small-cell carcinoma of the lung were treated with cyclophosphamide (160-200 mg/kg) ABMT followed by radiotherpay (4000 rads) to the primary site and mediastinum. Of the 19 patients evaluated at least 4 months after treatment, 15 (79 percent) developed radiologic evidence of fibrosis compared with only 35 percent of 20 consecutive patients treated with identical radiotherapy but standard doses of combination chemotherapy.

Results of some studies suggest that these extramedullary dose-limiting toxicities will permit only moderate increases in doses of cytotoxic agents to levels unlikely to have a major impact on resistant tumors (7). Data from studies in non-Hodgkin's lymphoma, where the best results have been achieved, suggest that the preparative treatment regimens currently used, can ablate the tumor in only 25 percent of patients. Thus, a significant number of patients would relapse, even if the autologous marrow could be purged (10).

The possible presence of marrow invasion may not be detectable in a significant

fraction of random marrow aspirates. Although it is feasible to obtain tumor free marrow from patients with solid tumors despite prior marrow involvement, in the case of hematologic malignancies, there is no absolute way to eliminate clonogenic tumor cells from the marrow suspension and reinfusion of tumor cells remains a risk for treatment failure. Identifying the cause of a relapse is not possible but often thought to be a failure of effectiveness of the cytoreductive regimens (11).

While the use of ABMT has allowed high-dose chemo-radiotherapy to be given to cancer patients without the development of irreversible or protracted marrow aplasia, there is difficulty in assessing whether any increased therapeutic effect is obtained by these escalated doses. The hypothesis that large doses greatly increase tumor destruction (steep dose-response curves) has not been supported or refuted by clinicai evidence (44,45).

The National Institutes of Health (NIH) has concluded that the use of ABMT in the treatment of leukemias has not been shown to produce results that are superior to that of conventional chemotherpy. They indicated that ABMT appears to produce more complete response rates in non-Hodgkin's and Burkitts lymphomas with long-term survivors than conventional chemotherapy. However, the followup time is still too short to enable a definitive determination to be made regarding these latter two conditions.

According to the NIH, the efficacy of ABMT in the treatment of other solid tumors remains to be proven.

Personal communication from E.D. Thomas (46), who is generally regarded as the foremost authority in the field of bone marrow transplantation, suggests that several more years will be required to establish a better critera for patient selection, the optimal cytotoxic regimens as well as the most appropriate in-vitro treatment of the marrow, all of which warrant continued investigation in clinical trials.

Despite reports of better tumor responses and occassional long-term survivors of ABMT, the responses have often been transient and most patients eventually relapse and die. A major challenge for chemotherapy appears to be the finding more effective drugs

rather than attempting to increase effectiveness by manipulating doses used to treat insensitive tumors (17).

SUMMARY

Autologous bone marrow transplantation is a technique for restoring bone marrow stem cells using the patients own previously stored marrow. The procedure is performed following lethal bone marrow aplasia associated with high-dose chemo-radiotherapy used in the treatment of various malignancies. It has been firmly established that the use of ABMT can safely and effectively provide hematopoietic reconstitution in marrow-ablated patients. However the procedure is very costly and its use is limited to relatively few centers that have the requisite expertise in both the pre and post-treatment management of these patients.

In some disease categories such as non-Hodgkin's lymphoma, neuroblastoma, small cell carcinoma of the lung, ABMT enhanced the long-term survival of patients who would not have been expected to do well on conventional therapy. However, proper selection of patients, optimum pre-transplant treatment regimens, efficacy of in-vitro purging techniques, and further followup for responding patients will require more study to determine the efficacy of this combined treatment which for the present is regarded by the clinical and scientific community as being investigational.

The clinical trials published to date have not provided definitive evidence of the relative efficacy of ABMT plus high-dose chemoradiotherapy as compared with standard treatments for malignant diseases. The results of carefully planned multicenter trials should resolve these issues of safety and efficacy.

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16. Abstract (Limit: 200 words)

Autologous bone marrow transplantation is a technique for restoring bone marrow stem cells using the patients own previously stored marrow. The procedure is performed following lethal bone marrow aplasia associated with high-dose chemo-radiotherapy used in the treatment of various malignancies. It has been firmly established that the use of ABMT can safely and effectively provide hematopoietic reconstitution in marrow-ablated patients. However, the procedure is very costly and its use is limited to relatively few centers that have the requisite expertise in both the pre and post-treatment management of these patients. In some disease categories such as non-Hodgkin's lymphoma, neuroblastoma, small cell carcinoma of the lung, ABMT enhanced the long-term survival of patients who would not have been expected to do well on conventional therapy. However, proper selection of patients, optimum pre-transplant treatment regimens, efficacy of in-vitro purging techniques, and further followup for responding patients will require more study to determine the efficacy of this combined treatment which for the present is regarded by the clinical and scientific community as being investigational. The clinical trials published to date have not provided definitive evidence of the relative efficacy of ABMT plus high-dose chemoradiotherapy as compared with standard treatments for malignant diseases. The results of carefully planned multicenter trials should resolve these issues of safety and efficacy.

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